

THAT WHICH IS CLAIMED:

1. A human monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said 5 monoclonal antibody being free of significant agonist activity, wherein said monoclonal antibody exhibits increased anti-tumor activity relative to an equivalent amount of the monoclonal chimeric anti-CD20 monoclonal antibody IDEC-C2B8, wherein said anti-tumor activity is assayed in a staged nude mouse xenograft tumor model using the Daudi human B cell lymphoma cell line.

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2. The human monoclonal antibody of claim 1, wherein said antibody is selected from the group consisting of:

- a) the monoclonal antibody CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 12.12,

15 deposited with the ATCC as Patent Deposit No. PTA-5543;

c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

d) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

25 e) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

f) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

- g) a monoclonal antibody that competes with the monoclonal antibody

30 CHIR-12.12 in a competitive binding assay;

h) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-g), wherein said antibody is recombinantly produced; and
5 i) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-h), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

3. The monoclonal antibody of claim 1, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

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4. A hybridoma cell line capable of producing the monoclonal antibody of claim 1.

5. A method for treating a cancer characterized by expression of CD40, comprising administering to a human patient an effective amount of a human anti-CD40 monoclonal antibody of claim 1.

6. The method of claim 5, wherein said cancer is selected from the group consisting of a non-Hodgkins lymphoma, chronic lymphocytic leukemia, multiple myeloma, B cell lymphoma, high-grade B cell lymphoma, intermediate-grade B cell lymphoma, low-grade B cell lymphoma, B cell acute lymphoblastic leukemia, myeloblastic leukemia, and Hodgkin's disease.

7. A human monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said monoclonal antibody being free of significant agonist activity, whereby, when said monoclonal antibody binds to the CD40 antigen expressed on the surface of said cell, the growth or differentiation of said cell is inhibited, wherein said antibody is selected from the group consisting of:

30 a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;

b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;

5 d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

10 e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

15 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

20 g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

25 i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

26 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

8. The antigen-binding fragment of claim 7, wherein said fragment is selected from the group consisting of a Fab fragment, an F(ab')₂ fragment, an Fv fragment, and a single-chain Fv fragment.

5 9. The monoclonal antibody of claim 7, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10⁻⁶ M to about 10⁻¹² M.

10 10. An isolated nucleic acid molecule comprising a polynucleotide that encodes an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8.

11. A hybridoma cell line capable of producing a human monoclonal antibody having specificity for a human CD40 antigen expressed on the surface of a human CD40-expressing cell, whereby said monoclonal antibody is free of significant agonist activity, whereby, when said monoclonal antibody binds to the CD40 antigen expressed on the surface of said cell, the growth or differentiation of said cell is inhibited, and wherein said monoclonal antibody is selected from the group consisting of:

20 a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in 25 SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in 30 SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ

ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay; and,
- j) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of a)-i), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

12. A method for inhibiting growth or differentiation of a normal human B cell, comprising contacting said B cell with an effective amount of a human anti-CD40 monoclonal antibody selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
- d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in

SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

e) a monoclonal antibody having an amino acid sequence encoded by a

5 nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

10 g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

i) a monoclonal antibody that competes with the monoclonal antibody

15 CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

20 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

25 13. The method of claim 12, wherein said monoclonal antibody or fragment thereof binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

30 14. The method of claim 12, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

15. A method for inhibiting proliferation of a normal human B cell, wherein
said proliferation is augmented by the interaction of a CD40 ligand with a CD40 antigen
expressed on the surface of said B cell, said method comprising contacting said B cell
5 with an effective amount of a human anti-CD40 monoclonal antibody selected from the
group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or
12.12;
- 10 c) a monoclonal antibody comprising an amino acid sequence selected from
the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in
SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ
ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID
NO:8;
- 15 d) a monoclonal antibody comprising an amino acid sequence selected from
the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in
SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ
ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID
NO:5;
- 20 e) a monoclonal antibody having an amino acid sequence encoded by a
nucleic acid molecule comprising a nucleotide sequence selected from the group
consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID
NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;
- f) a monoclonal antibody that binds to an epitope capable of binding the
25 monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87
of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- h) a monoclonal antibody that binds to an epitope comprising residues 82-89
of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- 30 i) a monoclonal antibody that competes with the monoclonal antibody
CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and
5 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

10 16. The method of claim 15, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

15 17. The method of claim 15, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

20 18. A method for inhibiting antibody production by B cells in a human patient, comprising administering to a human patient an effective amount of a human anti-CD40 monoclonal antibody or fragment thereof selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from 25 the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
- d) a monoclonal antibody comprising an amino acid sequence selected from 30 the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ

ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

5 e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

10 g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

15 i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

19 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen;

20 said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

19. The method of claim 18, wherein said monoclonal antibody binds to said 25 human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

20. The method of claim 18, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

21. A method for inhibiting growth of cancer cells of B cell lineage, comprising contacting said cancer cells with an effective amount of a human anti-CD40 monoclonal antibody selected from the group consisting of:

5 a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;

b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ

10 ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;

d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ

15 ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID

20 NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

25 h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

30 j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

22. The method of claim 21, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

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23. The method of claim 21, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

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24. The method of claim 21, wherein the cancer is selected from the group consisting of non-Hodgkins lymphoma, chronic lymphocytic leukemia, multiple myeloma, B cell lymphoma, high-grade B cell lymphoma, intermediate-grade B cell lymphoma, low-grade B cell lymphoma, B cell acute lymphoblastic leukemia, myeloblastic leukemia, and Hodgkin's disease.

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25. A method for treating an autoimmune disease, comprising administering to a human patient an effective amount of a human anti-CD40 monoclonal antibody selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;

5 d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

10 e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

15 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

20 g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

25 h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

15 i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

20 j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

25 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

26. The method of claim 25, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

27. The method of claim 25, wherein said fragment is selected from the group consisting of a Fab fragment, an F(ab')₂ fragment, an Fv fragment, and a single-chain Fv fragment.

5 28. The method of claim 25, wherein said autoimmune disease is selected from the group consisting of systemic lupus erythematosus, autoimmune thrombocytopenic purpura, Rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, myasthenia gravis, and pemphigus vulgaris.

10 29. A method for treating a cancer characterized by expression of CD40, comprising administering to a human patient an effective amount of a human anti-CD40 monoclonal antibody selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- b) the monoclonal antibody produced by the hybridoma cell line 5.9 or

15 12.12;

- c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID

20 NO:8;

- d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID

25 NO:5;

- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

30 f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

5 i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

10 k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen; said antibody or fragment thereof being free of significant agonist activity, and whereby when said antibody or fragment thereof binds to said CD40 antigen on said B cell, the growth or differentiation of said B cell is inhibited.

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30. The method of claim 29, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

31. The method of claim 29, wherein said fragment is selected from the group 20 consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

32. A method for identifying an antibody that has antagonist activity toward 25 CD40-expressing cells, comprising performing a competitive binding assay with a monoclonal antibody selected from the group consisting of:

a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;

b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

c) a monoclonal antibody comprising an amino acid sequence selected from 30 the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ

ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;

5 d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

10 e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

15 g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12; and

20 i) the monoclonal antibody of preceding item a) or a monoclonal antibody of any one of preceding items c)-h), wherein said antibody is recombinantly produced; and

j) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of a)-i), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

33. An antagonist anti-CD40 monoclonal antibody that specifically binds

25 Domain 2 of CD40.

34. The monoclonal antibody of claim 33, wherein said antibody is a human antibody.

30 35. The monoclonal antibody of claim 34, wherein said antibody is free of significant agonist activity.

36. The monoclonal antibody of claim 33, wherein said antibody has the binding specificity of an antibody selected from the group consisting of the antibody produced by hybridoma cell line 5.9 and the antibody produced by hybridoma cell line
5 12.12.

37. The monoclonal antibody of claim 33, wherein said antibody is selected from the group consisting of the antibody produced by hybridoma cell line deposited with the ATCC as Patent Deposit No. PTA -5542 and hybridoma cell line deposited with the
10 ATCC as Patent Deposit No. PTA-5543.

38. The monoclonal antibody of claim 33, wherein said antibody has the binding specificity of monoclonal antibody CHIR-12.12 or CHIR-5.9.

15 39. The monoclonal antibody of claim 33, wherein said antibody binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12.

20 40. The monoclonal antibody of claim 33, wherein said antibody is selected from the group consisting of:

25 a) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

b) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

30 c) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 12.12;

- d) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- e) a monoclonal antibody that competes with the monoclonal antibody CHIR-12.12 in a competitive binding assay; and

5 f) a monoclonal antibody that is an antigen-binding fragment of the CHIR-12.12 monoclonal antibody or the foregoing monoclonal antibodies in preceding items (a)-(e), where the fragment retains the capability of specifically binding to the human CD40 antigen.

10 41. A method for inhibiting a CD40 ligand-mediated CD40 signaling pathway in a human CD40-expressing cell, said method comprising contacting said cell with an effective amount of a human anti-CD40 monoclonal antibody selected from the group consisting of:

- a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;
- 15 b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ 20 ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;
- d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ 25 ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;
- e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID 30 NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

- f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;
- g) a monoclonal antibody that binds to an epitope comprising residues 82-87 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- 5 h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;
- i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;
- j) the monoclonal antibody of preceding item a) or a monoclonal antibody of 10 any one of preceding items c)-i), wherein said antibody is recombinantly produced; and
- k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

15 42. The method of claim 41, wherein said monoclonal antibody binds to said human CD40 antigen with an affinity (K_D) of at least about 10^{-6} M to about 10^{-12} M.

20 43. The method of claim 41, wherein said fragment is selected from the group consisting of a Fab fragment, an $F(ab')_2$ fragment, an Fv fragment, and a single-chain Fv fragment.

25 44. The method of claim 41, wherein said human CD40-expressing cell is a normal human B cell or a malignant human B cell and said CD40 signaling pathway is B cell survival.

45. A pharmaceutical composition comprising a human monoclonal antibody that is capable of specifically binding to a human CD40 antigen expressed on the surface of a human CD40-expressing cell, said monoclonal antibody being free of significant agonist activity, wherein said antibody is selected from the group consisting of:

30 a) the monoclonal antibody CHIR-5.9 or CHIR-12.12;

b) the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

c) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:6, the sequence shown in 5 SEQ ID NO:7, the sequence shown in SEQ ID NO:8, both the sequence shown in SEQ ID NO:6 and SEQ ID NO:7, and both the sequence shown in SEQ ID NO:6 and SEQ ID NO:8;

d) a monoclonal antibody comprising an amino acid sequence selected from the group consisting of the sequence shown in SEQ ID NO:2, the sequence shown in 10 SEQ ID NO:4, the sequence shown in SEQ ID NO:5, both the sequence shown in SEQ ID NO:2 and SEQ ID NO:4, and both the sequence shown in SEQ ID NO:2 and SEQ ID NO:5;

e) a monoclonal antibody having an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group 15 consisting of the sequence shown in SEQ ID NO:1, the sequence shown in SEQ ID NO:3, and both the sequence shown in SEQ ID NO:1 and SEQ ID NO:3;

f) a monoclonal antibody that binds to an epitope capable of binding the monoclonal antibody produced by the hybridoma cell line 5.9 or 12.12;

g) a monoclonal antibody that binds to an epitope comprising residues 82-87 20 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

h) a monoclonal antibody that binds to an epitope comprising residues 82-89 of the human CD40 sequence shown in SEQ ID NO:10 or SEQ ID NO:12;

i) a monoclonal antibody that competes with the monoclonal antibody CHIR-5.9 or CHIR-12.12 in a competitive binding assay;

j) the monoclonal antibody of preceding item a) or a monoclonal antibody of 25 any one of preceding items c)-i), wherein said antibody is recombinantly produced; and

k) a monoclonal antibody that is an antigen-binding fragment of a monoclonal antibody of any one of preceding items a)-j), wherein said fragment retains the capability of specifically binding to said human CD40 antigen.

46. The pharmaceutical composition of claim 45, wherein said composition is a liquid pharmaceutical formulation comprising a buffer in an amount to maintain the pH of the formulation in a range of about pH 5.0 to about pH 7.0.

5 47. The pharmaceutical composition of claim 46, wherein said formulation further comprises an isotonizing agent in an amount to render same composition near isotonic.

10 48. The pharmaceutical composition of claim 47, wherein said isotonizing agent is sodium chloride, said sodium chloride being present in said formulation at a concentration of about 50 mM to about 300 mM.

15 49. The pharmaceutical composition of claim 48, wherein said sodium chloride is present in said formulation at a concentration of about 150 mM.

50. The pharmaceutical composition of any one of claims 46 to 49, wherein said buffer is selected from the group consisting of succinate, citrate, and phosphate buffers.

20 51. The pharmaceutical composition of claim 50, wherein said formulation comprises said buffer at a concentration of about 1 mM to about 50 mM.

52. The pharmaceutical composition of claim 51, wherein said buffer is sodium succinate or sodium citrate at a concentration of about 5 mM to about 15 mM.

25 53. The pharmaceutical composition of any one of claims 46 to 52, wherein said formulation further comprises a surfactant in an amount from about 0.001% to about 1.0%.

54. The pharmaceutical composition of claim 53, wherein said surfactant is polysorbate 80, which is present in said formulation in an amount from about 0.001% to about 0.5%.